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November 30, 1998

Dr. Larry G. Hart
Executive Secretary
Board of Scientific Counselors
National Toxicology Program
P.O. Box 12233
Research Triangle Park, N.C. 27709

Dear Dr. Hart:

We are pleased to submit for the Board of Scientific Counselors' review the comments of the Health Effects Institute on the National Toxicology Program's (NTP) *Draft Report on Carcinogens Background Document for Diesel Exhaust Particulate Matter* that will be discussed at the December 2-3, 1998 Board meeting.

The Health Effects Institute (HEI) has had a longstanding involvement in diesel emissions including (1) an extensive research program on the health effects of diesel exhaust and its constituents, (2) a comprehensive review of diesel exhaust carcinogenicity that was published in an HEI Special Report (*Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects*, 1995), and (3) our ongoing Diesel Epidemiology Program, which includes the work of an Expert Panel that is evaluating the use of existing epidemiologic data for quantitative risk assessment and feasibility studies that we hope will lead to a major new epidemiologic study.

We are pleased that the products of many of HEI's efforts have been incorporated into the NTP's report on diesel exhaust particulates. In most cases, the authors of the report have cited the journal reference for HEI-funded studies (e.g., Nikula et al. 1995). We would like to bring to your attention the companion HEI Research Reports (in the above cited case, Mauderly et al. 1994) that are published for every HEI-funded research project. The HEI Research Reports include the investigator's report, which undergoes a rigorous peer-review by the Institute's Health Review Committee, and the Committee's commentary on the strengths and limitations of the work as well as its regulatory implications. The HEI Research Reports, which are listed on MEDLINE and NTIS, contain a complete account of the investigator's research (including negative as well as positive findings), are designed to meet the needs of regulators, and are accepted as peer-reviewed publications by regulatory decisionmakers. We will send, by separate mailing, those reports relevant to diesel exhaust and hope that the NTP will find them useful in revising its report.

We would also like to draw your attention to the abovementioned HEI Special Report, *Diesel*

Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. The HEI Diesel Working Group, which prepared the report, was chaired by Dr. Gareth Green and consisted of leading experts in the areas of diesel emissions, exposure assessment, toxicology, epidemiology, and carcinogenesis. Members of the Working Group prepared background papers (one of which, Cohen and Higgins is cited in the NTP Report) which underwent peer review and formed the basis for further discussion and evaluation by the Working Group. The Working Group's conclusions were presented in Part I of the report, "Critical Issues in Assessing the Carcinogenicity of Diesel Exhaust: A Synthesis of Current Knowledge" and in the Executive Summary. We think that a citation of the HEI Diesel Report and further examination of the Working Group's conclusions would be a useful addition to any comprehensive review of the health effects of diesel exhaust particulate matter.

Additional suggestions for improving the NTP Report on Diesel Exhaust Particulates are as follows:

Physical and Chemical Properties (1.1 - 1.3)

The information presented in this section is based almost entirely on emissions data from 1980s engines. As a result of regulatory actions, there have been major changes in diesel engine technology and fuel formulation over the last decade resulting in substantial reductions in diesel particulates and associated organic material. These changes may have significant implications for the carcinogenicity of diesel exhaust, since most studies of emissions from newer engines equipped with a catalyst have found a disproportionately higher reduction in organic components of exhaust than in other components.

Given these changes, we recommend that this section be updated to include emissions data from engines built after 1990, including a discussion of the impact of reformulated and low-sulfur fuels. Also, it would be helpful for any assessment of health risks to place the animal and human data (both of which have been derived almost entirely from engines built in the 1980s and, in the case of the animal data, from light-duty engines) in the context of the exposures from engines in use today and those predicted for the future.

There are some sources of information on diesel engine emissions that might be helpful in revising this chapter:

- *Characterization of Fuel and Aftertreatment Device Effects on Diesel Emissions.* ST Bagley, KJ Baumgard, SD Gratz, JH Johnson, DG Leddy. HEI Research Report Number 76. 1976.
  The investigators compared emissions from 1988 and 1991 heavy-duty engines using conventional and low-sulfur diesel fuel. They also studied the effects of an oxidation catalyst and a ceramic particle trap on particulate matter and chemical emissions.

- *Formation and Characterization of Particles: Report of the 1996 HEI Workshop.* HEI Communications Number 5. 1997.
  This report may be useful in providing sources of recent emissions data.

- *Motor Vehicle-Related Air Toxics Study.* U.S. EPA, Office of Mobile Sources. 1993.
  This document contains an extensive analysis of exposure estimates for diesel particulate matter based on calculations of emission rates and diesel vehicle miles traveled. We understand that it is currently being updated to provide estimates from current model engines using assumptions about the rate of penetration of such vehicles into the fleet.

- *Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant: Part A. Exposure Assessment.* California Environmental Protection Agency/Air Resources Board. June 1998.

Human Exposure (2.1 - 2.4)

There is more information on environmental exposures to diesel exhaust particulate matter than acknowledged in this section. The chapter by Glen R. Cass and H. Andrew Gray, "Regional Emissions and Atmospheric Concentrations of Diesel Engine Particulate matter" in the HEI Diesel Report and the reference cited above by the California Environmental Protection Agency/Air Resources Board are two examples of recent reviews.

Human Studies (3)

The HEI Diesel Working Group reached the following conclusions regarding human responses to diesel engine exhaust (*Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects 1995. HEI Special Report p.6.)*

- "The epidemiologic data are consistent in showing weak associations between exposure to diesel exhaust and lung cancer. The available evidence suggests that long-term exposure to diesel exhaust in a variety of occupational circumstances is associated with a 1.2- to 1.5-fold increase in the relative risk of lung cancer compared with workers classified as unexposed."

- "Despite the concern that confounding by cigarette smoke might explain the observed risk elevations, most studies that controlled for smoking found that the association between increased risk of lung cancer and exposure to diesel emissions persisted after such controls were applied, although in some cases, the excess risk was lower. Only a few epidemiologic studies considered other potential confounders such as non-diesel particles, environmental tobacco smoke, asbestos exposure, diet and socioeconomic factors. At present, there is insufficient evidence to conclude whether confounding by these factors influenced the results."

- "As is frequently the case in epidemiologic studies of air pollutants, none of the studies measured exposure to diesel emissions or characterized the actual emissions from the source of exposure for the period of time most relevant to the development of lung cancer. Most investigators classified exposure on the basis of work histories reported by the subjects or their next of kin, or by retirement

records. Although these data provide relative rankings of exposure, the absence of concurrent exposure information is the key factor that limits interpreting the epidemiologic findings and using them to make quantitative estimates of cancer risk."

Experimental Carcinogenesis (4.1 - 4.3)

This section and the Summary Statements do an excellent job of presenting the recent literature and discussing possible mechanisms of particle-induced lung tumors in rats. However, these sections do not fully capture the state of the science on how this response should be used for hazard identification because no mention is made of the lung overload response to the high-dose exposure regimen, nor are these results put in the context of typical human exposures. It is now generally agreed that chronic inhalation of high concentrations of poorly soluble particles leads to lung overload resulting in pulmonary inflammation, fibrosis, epithelial hyperplasia, and, in some instances, adenomas and carcinomas in the peripheral lung of rats. There is an apparent threshold for all of the above responses. The animal studies consistently show that lung tumor induction in rats requires prolonged exposure to concentrations of diesel exhaust particulate matter in excess of 1,000 µg/m3. (Ambient exposures are in the 1 - 10 µg/m3 range; most occupational exposures range from 10 - 100 µg/m3, with the exception of underground mines, where some exposures are higher.) The International Life Sciences Institute - Risk Sciences Institute conducted a Workshop in March 1998 on the "Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment." The report from that Workshop, which is expected to be issued within the next few months, should be helpful in revising this section.

Genotoxicity (5.1 - 5.4)

There are three relevant HEI Research Reports that would inform the discussion of section 5.3.1 and 5.3.2. These reports should be consulted and cited in the NTP Report because they contain more complete information on the neoplastic and genotoxic responses than found in the journal articles and, in one important case (Randerath et al. 1995), the genotoxicity results were negative.

- Pulmonary Toxicity of Inhaled Diesel Exhaust and Carbon Black in Chronically Exposed Rats. HEI Research Report Number 68

  Part I: Neoplastic and Nonneoplastic Lung Lesions. JL Mauderly et al. 1994.

  This 100-page report contains complete details of the study later published by Nikula et al. in *Fundam. Appl. Toxicol.* 1995, including DNA adduct data.

  Part II: DNA Damage. K Randerath et al. 1995.

  Dr. Randerath is one of the leading experts on the use of ^{32}P-postlabeling to identify DNA adducts. He found that only endogenous DNA adducts (not diesel-specific adducts) were increased in the lungs of rats exposed to high concentrations of diesel exhaust. This report contains the results of the most exhaustive analysis of DNA adducts in diesel-exposed rats that has been conducted to date and provides additional support for the conclusion that

particles *per se*, and not the adsorbed organic compounds, are responsible for the lung tumors produced in rats following prolonged exposure to high concentrations of diesel emissions. The study also employed a more rigorous statistical approach to assure the symmetric distributions needed for statistical data analysis than previously published studies in this area.

Part III. Examination of Possible Target Genes. SA Belinsky et al. 1995. No significant increase in the frequency or pattern of K-*ras* or *p53* mutations in rat lung tumors induced by diesel engine exhaust was found.

With regard to the genotoxicity of diesel emissions, there are three factors that need to be considered: (1) the genotoxicity of the adsorbed organic compounds, (2) the genotoxicity of atmospheric transformation products, and (3) the biovailability of the organic compounds. It is well established that solvent extracts of diesel exhaust particulate matter are mutagenic in bacterial and mammalian systems *in vitro*. What is not known is what fraction of this material is bioavailable and what fraction remains adsorbed on the particle.

In our view, the NTP Report could be improved if the authors tried to integrate the toxicology, epidemiology, and exposure data. We recognize that this is a challenge because (1) diesel emissions have changed over the last two decades and will continue to change as a consequence of improvements in fuels and technology, (2) questions about the relevance of the rat lung tumor response, and (3) the limitations in exposure assessment for the epidemiology studies. At the present time, there is an apparent disconnect among the human, animal, and in vitro data. In particular, the agent (particles) and mechanisms responsible for diesel exhaust-induced lung tumors in rats do not appear to be those responsible for the human response. It would be helpful if the NTP Report addressed whether there is a risk of exposure to ambient levels of emissions from today's diesel engines, and if so, how can that risk best be characterized.

HEI appreciates the opportunity to submit these comments and looks forward to answering any further questions that you might have.

Sincerely,

Daniel S. Greenbaum
President

Kathleen M. Nauss, Ph.D.
Director for Scientific Review
and Evaluation